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Development of the human fetal testis

Développement testicule fœtal chez l'homme

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Abstract

Masculinisation and adult fertility in the male are dependent on appropriate fetal endocrine programming. There is also now increasing evidence to indicate that the same mechanisms which regulate masculinisation also affect the general wellbeing of males throughout their life and, particularly, during ageing. Testosterone, secreted by the fetal testes, is the main factor regulating these processes and an understanding of fetal testis development in the human male is essential if we are to prevent adult reproductive disorders. This review focuses on what is known about human testis development and describes the effects of maternal smoking, a surrogate of possible xenotoxicant exposure on fetal testis and fetal liver function.

Keywords: Human; Fetal; Liver; Testis; Steroidogenesis; Maternal smoking

Résumé

La masculinisation et la fertilité de l'homme à l'âge adulte sont dépendantes d'une programmation fœtale endocrine appropriée. Il existe également maintenant des preuves croissantes que ces mêmes mécanismes qui régulent la masculinisation affectent aussi le bien-être général des sujets masculins tout au long de leur vie, y compris au cours du vieillissement. La testostérone, sécrétée par les testicules fœtaux, en constitue le principal facteur régulateur et la compréhension du développement du testicule fœtal chez le sujet masculin est essentielle à la prévention des troubles de la reproduction chez l'adulte. Cette revue est focalisée sur ce que l'on sait du développement du testicule fœtal. Elle décrit les conséquences du tabagisme maternel en tant que possible marqueur de l'exposition aux perturbateurs endocriniens sur le testicule fœtal et la fonction hépatique fœtale.

Mots clés : Homme ; Fœtus ; Foie ; Stéroïdogenèse ; Tabagisme maternel

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1. Introduction

Following the epidemiological studies of Barker et al. in the 1980s, it has become clear that adult health and wellbeing are critically dependent on the environment experienced during fetal development [1]. The key to understanding many adult disorders is likely to be dependent upon knowledge of how an individual's adult phenotype is shaped during development and how these processes can be deregulated. In the male, masculinisation and adult fertility are dependent on appropriate fetal endocrine programming and there is now increasing evidence to indicate that the same mechanisms which regulate masculinisation also affect the general wellbeing of males throughout their life and, particularly, during ageing. Endocrine programming in the fetal male is mediated largely through testosterone secreted by the testes. Testosterone masculinises the fetal reproductive system by inducing growth and development of the Wolffian ducts, the accessory glands and male external genitalia. Disruption to this process will cause a spectrum of disorders ranging from pseudohermaphroditism to cryptorchidism and reduced adult sperm counts. An understanding of fetal testis development is a prerequisite, therefore, to understanding and preventing adult reproductive disorders. Animal models are invaluable for a mechanistic understanding of development but there are enough differences in testis development between humans and non-primate models to make it essential that we have a detailed knowledge and understanding of events in the human.

Testicular differentiation begins in the human at about 6 weeks after conception with the development of testicular cords containing Sertoli cells and gonocytes [2]. The Sertoli cells start secreting anti-Mullerian hormone (AMH) soon after differentiation, leading to the process of Mullerian duct regression, which is complete by mid gestation. Leydig cells can be seen in the interstitium of the fetal testis by week 8 [3,4] although the testes will show steroidogenic activity in vitro at 6–7 weeks [5]. Testosterone is detectable in the fetal circulation by week 8 reaching a peak around weeks 11–13 [6,7]. This period, towards the end of the first trimester and including the first half of the second trimester appears to be particularly important for normal reproductive development of the male fetus. This is when the presumptive masculinisation programming window (MPW) occurs in the human [8] – the period during which androgen action is essential to ensure normal masculinisation. Events dependent on androgen action during the MPW include normal development of the anogenital distance (AGD), penis formation and adult length, urethral development, testis descent and adult fertility [8,9].

This article describes basic studies from our lab and from others on the development of the human testis and available insights into regulatory mechanisms from natural mutations and from the effects of toxicant exposure in vivo through maternal smoking.

2. Cell development

Combined analysis of three separate studies, all of which used the unbiased optical dissector technique, have given us a clear view of developmental changes in human testis cell number during the first and second trimester (Fig. 1). Our studies have shown that fetal Sertoli cell number in the human doubles approximately every 2 weeks from week 7 of gestation to week 19 [10,11]. The rate of proliferation drops during the third trimester and Sertoli cell number doubles three more times to reach about 130×10^6 cells/testis at birth [12]. Leydig cell numbers increase exponentially during the first half of the second trimester reaching a maximum number of about 2×10^6 at 18 weeks [11]. Thereafter, Leydig cell numbers decline in the human fetus up until birth through a process of dedifferentiation or degeneration [13,14]. Germ cell numbers show an exponential increase during fetal development from the start of testis differentiation until the end of the second trimester [11]. The rate of increase in germ cell numbers is greatest from 6 weeks until 10 weeks and is then reduced until the end of the second trimester [15]. The reason for this slowing of germ cell proliferation after 10 weeks is not clear but may be related to the number of Sertoli cells. There is a clear increase in the germ cell/Sertoli cell ratio between the first and second trimester, caused by the slower proliferation rate of the Sertoli cells during the first trimester (Fig. 1) [11]. If germ cell numbers are dependent on Sertoli cell number during fetal development, as they are in the adult, then germ cell proliferation may be limited by Sertoli cell numbers during the second trimester. Gonocyte migration to the basement membrane and differentiation to spermatogonial stem cells (SSC) and spermatogonia commences towards the end of the second trimester in humans and lasts for up to 8 months post-natally [16]. The process is gradual and asynchronous in primates, which means that while spermatogonia form in fetal life, undifferentiated germ cells at different stages of development will still be present throughout fetal and neonatal development. The differentiation step from gonocyte to SSC is particularly important as it has been reported that carcinoma in situ (CIS) cells arise from arrested/dysfunctional gonocytes [17].

3. Control of development

In mammalian species for which we have data, initial development of the testis is independent of pituitary support. Thus, data available from the boar, rabbit, stallion, bull, ram, rat/mouse and dog would suggest that fetal Leydig cell function develops, at least initially, without a need for LH stimulation [18]. The hypothalamic-pituitary axis develops about halfway through gestation in most of these species and the testes become LH-dependent soon after [18]. In primates, including the human, the testes appear to go through an early phase of hormone-independence but, unlike other species, this is relatively short and the Leydig cells rapidly become dependent on the activity of chorionic gonadotrophin (CG) which acts to stimulate the LH-receptor (LHCGR). This is clear from humans with an inactivating mutation in the LHCGR or LHβ subunit. Individuals who are XY but lack LHCGR activity have an external female phenotype consistent with a lack of testicular androgen production during fetal development [19]. Remnants of some androgen-dependent structures (epididymis and ductus